DETAILED ACTION

Status of the Claims

Claim(s) 1-11 and 20-22 are pending. The following Office Action is in response to Applicant's communication dated December 13, 2007.

Claim Rejections - 35 USC § 103 - Withdrawn

Applicant's amendments and/or supplemental remarks regarding the rejection of claims 1-5, 10, 11, 20, and 21 over Antonarkis and Bao are sufficient to overcome the grounds of the rejection. None of the applied references expressly teach amplification of genomic DNA using two different primer pairs, one being targeted for a control gene, and one being targeted for a chromosome segment of interest, the chromosome being different from that of the chromosome of the control gene. Thus, the rejection has been withdrawn.

Claim Rejections - 35 USC § 103 - New Grounds

The following rejections are made in view of Applicant's amendments.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claim(s) 1-5, 9, 10, 11, 20, and 21, are rejected under 35 U.S.C. 103(a) as being unpatentable over Antonarakis et al. (U.S. 2003/0054386 A1) in view of Markoulatos et al. ("Multiplex polymerase chain reaction: a practical approach" J Clin Lab Anal. 2002;16(1):47-51), in further view of Lockhart et al. (U.S. 6,040,138), and in further view of in view of Bao et al. (U.S. 6,251,601 B1).

With regard to claim(s) 1, Antonarakis teaches methods of high throughput detection of chromosomal abnormalities ([0011]-[0030]; examples 2-4, for example). Specifically, Antonarkis teaches methods comprising: a) making a polymerase chain reaction (PCR) mixture ([0080]; [0117], for example) by mixing in a vessel components comprising: (i) eukaryotic genomic DNA [0075]; [0116], for example); (ii) a plurality of pairs of forward and reverse DNA primer oligonucleotides wherein one primer of each said pair is complementary to a 3' sequence of a targeted segment of a first DNA strand of the eukaryotic DNA and the other primer is complementary to the 3' sequence of the second strand of the targeted segment, the length of the segment of eukaryotic DNA being between about 50 and about 300 base pairs ([0053]; [0117], for example), wherein one of the primers of each pair has a detectable label attached to its 5' end ([0079]; i.e. primers with detectable labels; primers necessarily have a free 3'OH and thus, since there is no definition of the term 5'end, any detectable label contained within the primer sequence can be considered attached to the 5'-end), and wherein a plurality of the pairs of primers are each targeted to a segment of a

selected different chromosome of interest which is indicative of a potential chromosomal disorder and one pair is targeted for a segment of a control gene which is present on a chromosome other than one on which there is a targeted segment and does not target any chromosome segment that might be indicative of a potential aneuploidy ([0015]-[0028]; [0116], SIM2 and SIM1 on chromosome 21 and 6, respectively, testing for trisomy 21, for example); and iii. PCR buffers and enzymes necessary to carry out PCR amplification; b) conducting a PCR for between about 5 and about 60 temperature cycles to create amplified PCR products ([0117], 35 cycles, for example).

With regard to claim(s) 3 and 4, Antonarakis teaches detection of DiGeorge's and Down's syndrome (table 2, for example).

With regard to claim(s) 5, Antonarakis teaches fluorescent labels ([0079]; for example).

It is noted that Antonarakis teaches the use of paralogous gene sets (table 1, for example) to determine chromosomal abnormalities (fig. 9, for example) so that identical primers can be used to amplify both genes on the separate chromosomes ([0112]-[0113], for example); however, it is submitted that the concept behind the detection methods of Antonarakis and the instant invention are the same, as demonstrated by the teachings of Antonarakis, which highlight that, "Deviations from a 1:1 ratio of target to reference gene indicates an individual at risk for a chromosomal abnormality ([0085] and [0088], for example).

Due to the sequence homology of the paralogous genes, Antonarakis chooses sequencing methods to determine the copy number based ratio needed

to determine if a chromosomal abnormality is present ([0082]-[0086], for example), and thus, does not expressly teach the use of microarrays to detect gene copy numbers as required by steps d-g of claimed invention. Furthermore, Antonarakis does not expressly teach amplification of genomic DNA using two different primer pairs, one being targeted for a control gene, and one being targeted for a chromosome segment of interest, the chromosome being different from that of the chromosome of the control gene, i.e. a multiplex PCR of two different loci on two different chromosomes.

With regard to multiplex PCR, it is submitted that multiplex PCR was well known in the art at the time of invention. Markoulatos provides a contemporary review highlighting the time saving aspect of the procedure (abstract, for example).

With regard to the use of microarrays and a single control gene, it is first submitted that the use of microarrays for the parallel examination of high numbers of gene sequences was well known in the art at the time of invention. Lockhart provides a supportive disclosure that teaches the use of microarrays to detect alterations in gene copy number through isolation and amplification of genomic DNA (col. 11, lines 50-60; col. 12, lines 15-20, for example). The reference further highlights GAPD as a common "housekeeping" gene used as a control on microarrays (col. 16, lines 30-65, for example). Thus, Lockhart demonstrates that GAPD was well known in the art to be an excellent control gene capable or providing a reliable base line for array detection procedures. It is further noted that the GAPD gene occurs on a different chromosome than a

segment chosen to detect DiGeorge's or Down's syndrome (chromosomes 12 and 21), and thus would require different primer pairs targeted to different chromosomes.

With regard to steps d-g of the claimed inventions, Bao provides a supporting disclosure that teaches methods of detecting chromosomal abnormalities, including that of Down's Syndrome (col. 18, lines 50-55, for example) through the use of microarrays (col. 2-3, for example).

Specifically, with regard to steps d-f, Bao teaches PCR amplification of sample DNA (col. 12, lines 20-30, for example), subsequent hybridization of single-stranded DNA to microarrays (col. 13, lines 30-60, for example), and array detection with result assessment as it relates to the presence or absence of a chromosomal disorder (col. 15-18, array detection, for example). As noted above, the use of microarrays for the parallel examination of high numbers of gene sequences was considered standard practice in the art at the time of invention. Bao specifically highlights that array target elements may be replicated several times to provide better results (col. 10, lines 35-50, for example).

Specifically, with regard to step g, Bao teaches comparison of genomic samples to detect aneuploidy (col. 18, copy numbers, deletions or additions, Down's or DiGeorege's syndrome, for example). Furthermore, with regard to the term "comparison," it is noted that without a specific definition within the claim or specification, this term is simply considered a mental step, as simply visualizing experimental results can be considered "comparing." In other words, the

combination of references provides all the necessary variables to obtain, at the very least, visual detection of a chromosomal abnormality. For example, a skilled artisan would have been able to visually compare, utilizing microarrays, a target region (microarray test spot from a test subject) with a control region (microarray control spot from a control gene), and a normal region homologous to the target region (microarray normal spot from a normal subject).

With regard to claim(s) 2, Bao teaches application of rule-based algorithms (col. 16, lines 15-35; col. 17, lines 10-20, for example).

With regard to claim(s) 10, Bao teaches probes of about 25 to about 60 nucleotides (col. 8, lines 25-35, for example).

With regard to claim(s) 11, Bao specifically highlights that array target elements may be replicated several times to provide better results (col. 10, lines 35-50, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to utilize microarrays to detect the chromosomal disorders detected through the methods of Antonarakis since the prior art demonstrates that such devices can be used to examine high numbers of gene sequences in parallel.

Furthermore, it would have been *prima facie* obvious to a skilled artisan at the time of invention to include a control gene spot on the microarrays since the prior art demonstrates that such spots are useful for obtaining normalized, accurate results. Also, it would have been obvious to simply amplify the target and control region through a multiplex PCR utilizing different primers since the

prior art demonstrates that such a method reduces experimental time. applicant is reminded that Bao teaches comparison of genomic samples to detect aneuploidy (col. 18, copy numbers, deletions or additions, Down's or DiGeorege's syndrome, for example).

With regard to claim(s) 20, specifically step g, and 21, while referring to "ratios" of microarray images, does not expressly require, or actively recite physical mathematical calculations, and thus, as is the case with step g of claim 1, is simply considered a collection of mental steps, as simply visualizing experimental results can be considered "comparing" (see discussion of claim 1 above). With regard to gender specific averages, Bao teaches the use of microarrays for genomic disease management, including diseases that are more likely to occur in one gender (e.g. breast cancer, females, for example). Thus, it would have been *prima facie* obvious to a skilled artisan to obtain averages from a specific gender.

2. Claim(s) 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Antonarakis et al. (U.S. 2003/0054386 A1) in view of Markoulatos et al. ("Multiplex polymerase chain reaction: a practical approach" J Clin Lab Anal. 2002;16(1):47-51), in further view of Lockhart et al. (U.S. 6,040,138), in further view of in view of Bao et al. (U.S. 6,251,601 B1) as applied claim 1 above, and in further view of Fulcrand et al. (U.S. 6,319,674 B1).

The methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach primer pairs, one having a phosphate group as well as one having a fluorescent group, and subsequent digestion of the phosphate labeled primer with an exonuclease.

Fulcrand provides a supporting disclosure that teaches methods of generating labeled single stranded DNA utilizing phosphate labeled primers (col. 26, lines 10-35, for example). Specifically, Fulcrand, teaches primer pairs, one having a phosphate (col. 26, lines 15-20, for example) group as well as one having a fluorescent group (col. 26, lines 15-20, Cy3, for example), and subsequent digestion of the phosphate labeled primer with an exonuclease (col. 26, lines 20-25, lamda exonuclease, for example).

In summary, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to incorporate primer pairs, one having a phosphate group as well as one having a fluorescent group, and subsequent digestion of the phosphate labeled primer with an exonuclease within microarray based assays since the prior art demonstrates such a method as able to produce labeled single stranded DNA for subsequent hybridization to microarrays.

Allowable Subject Matter

The following is a statement of reasons for the indication of allowable subject matter: Regarding claim 22, a search of the prior art found no reference

teaching or suggesting basing the detection of a chromosomal disorder by actively or physically calculating an A-ratio by dividing an I-ratio by a C-factor.

Conclusion

Claim(s) 1-11, 20, and 21 are rejected.

Claim 22 is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone

number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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